Interventional Cardiology

First Clinical Application of an Actively Reversible Direct Factor IXa Inhibitor as an Anticoagulation Strategy in Patients Undergoing Percutaneous Coronary Intervention

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Background—The ideal anticoagulant should prevent ischemic complications without increasing the risk of bleeding. Controlled anticoagulation is possible with the REG1 system, an RNA aptamer pair comprising the direct factor IXa inhibitor RB006 and its active control agent RB007.

Methods and Results—This phase 2a study included a roll-in group (n=2) treated with REG1 plus glycoprotein IIb/IIIa inhibitors followed by 2 groups randomized 5:1 to REG1 or unfractionated heparin. In group 1 (n=12), RB006 was partially reversed with RB007 after percutaneous coronary intervention and fully reversed 4 hours later. In group 2 (n=12), RB006 was fully reversed with RB007 immediately after percutaneous coronary intervention. Femoral sheaths were removed after complete reversal. Patients were pretreated with aspirin and clopidogrel. End points included major bleeding within 48 hours; composite of death, myocardial infarction, or urgent target vessel revascularization within 14 days; and pharmacodynamic measures. All cases were successful, with final Thrombolysis in Myocardial Infarction grade 3 flow and no angiographic thrombotic complications. There were 2 ischemic end points in the REG1 group and 1 in the unfractionated heparin group, with 1 major bleed in the unfractionated heparin group. Median activated clotting time values rose from 151 to 236 seconds after RB006. Administration of the partial RB007 dose reversed anticoagulation to an intermediate activated clotting time value of 186 seconds. Complete reversal with RB007 returned the median activated clotting time value to 144 seconds. Both reversal strategies enabled scheduled femoral sheath removal.

Conclusions—This study demonstrates the clinical translation of a novel platform of anticoagulation targeting factor IXa and its active reversal to percutaneous coronary intervention and provides the basis for further investigation.


Key Words: angioplasty ■ anticoagulants ■ coronary disease ■ thrombosis

Percutaneous coronary intervention (PCI) is a widely used method of myocardial revascularization. A certain level of anticoagulation is required to perform elective PCI safely and to prevent procedural thrombosis and its attendant complications, including myocardial ischemia and infarction resulting from arterial injury after balloon inflation and stent placement. Anticoagulants used for PCI increase the risk of bleeding, particularly at femoral access sites. An unmet need in current practice is an anticoagulant and administration strategy that optimizes efficacy and safety.

Clinical Perspective on p 622

The emergence of a platform designed to generate drug-control agent pairs has been described. The REG1 system (Regado Biosciences Inc, Basking Ridge, NJ), an anticoagulant aptamer that selectively targets coagulation factor IXa and its matched active control agent, is the first of its kind.
kind to enter clinical testing. The anticoagulant component, RB006, is a 31-nucleotide nuclease-resistant RNA aptamer conjugated to a 40-kDa polyethylene glycol carrier that blocks the coagulation factor VIIIa/factor IXa catalyzed conversion of factor X to Xa. The active control agent, RB007, is a 15-nucleotide 2'-modified RNA oligonucleotide that binds RB006 in a complementary fashion, thereby controlling its pharmacodynamic activity. The nucleotide that binds RB006 in a complementary fashion, agent, RB007, is a 15-nucleotide 2'-modified RNA oligonucleotide that binds RB006 in a complementary fashion, thereby controlling its pharmacodynamic activity. The nucleotide that binds RB006 is 31-nucleotide nuclease-resistant RNA aptamer conjugated to a 40-kDa polyethylene glycol carrier that blocks the coagulation factor VIIIa/factor IXa catalyzed conversion of factor X to Xa. The active control agent, RB007, is a 15-nucleotide 2'-modified RNA oligonucleotide that binds RB006 in a complementary fashion, thereby controlling its pharmacodynamic activity.

Methods

Study Design and Treatments

This phase 2a, open-label, multicenter, randomized, feasibility, and safety study compared REG1 with unfractionated heparin (UFH) during PCI. The design (Figure 1) involved a roll-in group and a randomized group divided into 2 stages. The roll-in group included 2 patients and was incorporated into the study design to optimize the timing and performance of study-related procedures. This group was not included in the final data analyses. Because these 2 patients were the first to receive REG1 during PCI, they were concomitantly treated with an intravenous glycoprotein IIb/IIIa antagonist to enhance safety through rapid and effective platelet inhibition. In the roll-in group, 24 patients were allocated 5:1 to receive REG1 (RB006 followed by RB007) or UFH through the use of centralized Web-based randomization. Enrollment occurred in 2 stages exploring 2 post-PCI anticoagulation reversal strategies in patients assigned to REG1. In the first stage, RB006 was partially reversed by RB007 (0.2:1 active control:drug) immediately after PCI, followed by complete reversal (1.8:1 active control:drug) 4 hours later and sheath removal. The rationale of a partial reversal strategy was based on uncertainties about the optimal duration of anticoagulation after PCI. The 4-hour interval between partial and complete reversal was chosen to simulate current practice with UFH, which has a half-life of ~60 minutes at the dose used in PCI. In the second stage, RB006 was completely reversed by RB007 (2:1 active control:drug) after PCI and followed by sheath removal. In patients assigned to UFH, a 60- to 70-U/kg intravenous bolus was administered to achieve an activated clotting time (ACT) of 250 to 350 seconds; the femoral sheath was removed 4 hours after PCI or with an ACT <180 seconds. All patients were followed up through hospitalization and returned for a 14-day follow-up visit.

Dose selection was based on observed relationships between factor IXa inhibition, APTT, and drug plasma concentrations demonstrating nearly complete factor IXa inhibition with an RB006 dose of 1 mg/kg. The active control agent (RB007) dose was based on prior studies performed by our group demonstrating 50% (partial) and 100% (complete) anticoagulation reversal with 0.2:1 and 2:1 control agent:drug ratios.

All patients were pretreated with 250 to 500 mg aspirin and clopidogrel (600 mg in clopidogrel-naive patients, 300 mg in patients already on clopidogrel) administered no less than 4 hours before PCI. Aspirin (250 to 500 mg/d) and clopidogrel (75 mg/d) were continued throughout the study with a recommended duration of at least 1 year for clopidogrel and indefinitely for aspirin.

An independent Review Committee was chartered to monitor patient safety. Data were reviewed after completion of the roll-in and partial reversal groups. Special emphasis was placed on capturing thrombotic intraprocedural complications such as abrupt vessel closure, no reflow, and the formation of clots on or within the interventional equipment (catheters and wires). A specific UFH bailout strategy was included in the protocol to guide investigators in the event of a thrombotic complication.

The institutional review board at each institution approved the study; patients provided written informed consent before participa-
tion. The study was registered with ClinicalTrials.gov under the identifier NCT00715455.

**Patients**

Patients 18 to 80 years of age undergoing nonurgent single- or 2-native-artery PCI through a 6F femoral sheath were considered for inclusion. Exclusion criteria were weight >120 kg; recent (<7 days) acute coronary syndrome with elevated cardiac markers or ST-segment depression; ST-segment elevation myocardial infarction (MI) within 30 days; clinical instability; ejection fraction <40%; aortic dissection; significant valvular or congenital heart disease; severe persistent hypertension (>180/110 mm Hg); or high angiographic risk (left main or bifurcation disease, angiographic thrombus, complex lesion requiring multiple stents, total occlusion, saphenous vein graft lesion, heavily calcified lesion, lesion length >20 mm, and planned use of a stent longer than 25 mm); planned use of devices other than balloons and stents; hypercoagulable state; bleeding diathesis; contraindication to anticoagulation; prolonged cardiopulmonary resuscitation; recent (<3 months) severe trauma, major surgery, or biopsy of a parenchymal organ; recent gastrointestinal or genitourinary bleeding; prior stroke; hemoglobin <11.0 g/dL; elevated prothrombin time or APTT; creatinine clearance <50 mL/min; abnormal liver function studies; platelet count <100 000/mm³ or >600 000/mm³; previous use of thrombolytics (<30 days), low-molecular-weight heparin (<24 hours), and UFH (<4 hours); planned use of warfarin (<7 days); aspirin and/or clopidogrel allergy; and lactation or pregnancy.

**Outcome Measures and Definitions**

The primary outcome measures were major bleeding within 48 hours or through hospital discharge, whichever occurred first, and a composite of all-cause death, nonfatal MI, and urgent target vessel revascularization through 14 days. Secondary outcome measures were other clinical events; angiographic thrombotic complications; cardiovascular complications; vascular-access complications; and coagulation parameters, including plasma prothrombin time and APTT and point-of-care whole-blood APTT and ACT.

Major bleeding was defined as intracranial, retroperitoneal, intraocular or intraarticular, vascular access–related bleeding requiring intervention, hematoma ≥5 cm at the access site, reduction in hemoglobin >4 g/dL without an overt source or ≥3 g/dL with an overt source of bleeding, reoperation for bleeding, and transfusion of any blood product. Bleeding data were captured to classify bleeding according to other accepted definitions of bleeding.6,14 MI was defined as any elevation in cardiac enzyme kinetic or creatine kinase-MB levels ≥3 times the upper reference limit within 24 hours after PCI or ≥2 times the upper reference limit and ≥50% above the previous nadir in the presence of new ischemic symptoms or as new Q-waves ≥30 milliseconds in 2 contiguous ECG leads. Cardiac markers were assessed at baseline and 8, 16, and 24 hours after PCI and ECGs at baseline, 24 hours, and 14 days after randomization. Urgent target vessel revascularization was defined as any revascularization of the vessel treated during the index procedure as a result of acute myocardial ischemia.

**Coagulation Assessments**

ACT and point-of-care whole-blood APTT were assessed with a point-of-care device (Hemochron Junior Signature Elite Microcoagulation System, International Technidyne Corp, Edison, NJ). Plasma APTT and prothrombin time were assessed at each site laboratory. In the roll-in and partial reversal patients, ACT, point-of-care whole-blood APTT, plasma APTT, and prothrombin time were measured at baseline, before PCI (5 and 15 minutes after RB006), after PCI (5 and 15 minutes after partial reversal with RB007), 4 hours after PCI, before and after femoral sheath removal (5 and 15 minutes after complete reversal with RB007), and 24 hours after PCI. In the complete reversal group, these assessments occurred at baseline, before PCI (5 and 15 minutes after RB006), after PCI,

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LVEF indicates left ventricular ejection fraction; BP, blood pressure. Values are presented as median (25th, 75th percentiles) when appropriate.

**Statistical Analysis**

The sample size was decided without a formal calculation to assess the feasibility of using REG1 during PCI. Data are summarized as frequencies with percentages and medians with 25th and 75th percentiles. Because plasma APTT and prothrombin time were measured at the local sites with different reagents, these measures are presented as ratios calculated by dividing the value at a given time point after study drug administration by the baseline value. Plasma APTT and point-of-care whole-blood APTT ratios were plotted. To assess the relationship between these ratios, we constructed a linear mixed-effects model. A random effect for each subject was included to account for the correlation between measurements on the same subject. We used restricted cubic splines to assess whether the relationship between plasma APTT and point-of-care APTT ratios was linear. The relationship was found to be linear. Empirical SEs were used to allow the residuals to deviate from normality. All analyses were performed with statistical software (SAS Institute Inc, Cary, NC).

**Results**

**Patient and Procedural Characteristics**

A total of 26 patients were enrolled at 4 sites in the United States and 1 site in Argentina between October 2007 and October 2008. Baseline demographics are presented in Table 1. Median age was 64 years (25th and 75th percentiles, 59 and 67 years), and weight was 91 kg (25th and 75th percentiles, 83 and 101 kg); 67% were male; and 92% were white. All
patients received a median dose of 325 mg aspirin and 600 mg clopidogrel at 5.3 and 5.9 hours before PCI, respectively. Table 2 displays procedural characteristics. Of the 30 attempted lesions, 29 were successfully dilated (inability to cross lesion with the wire in 1 case). Stents were used in 28 lesions; drug-eluting stents were used in 50%; and 2-vessel PCI was performed in 6 cases. All procedures were performed through 6F femoral sheaths, with a median duration of 23.5 minutes (25th and 75th percentiles, 12 and 37 minutes), and final Thrombolysis in Myocardial Infarction grade 3 coronary flow in all cases. Femoral sheaths were removed at 281.5 minutes (25th and 75th percentiles, 266 and 308 minutes) after PCI in the partial reversal group, 46 minutes (25th and 75th percentiles, 42 and 52 minutes) in the complete reversal group, and 216.5 minutes (25th and 75th percentiles, 129.5 and 300 minutes) in the UFH group.

Coagulation and Safety Laboratory Measurements

Coagulation parameters are presented in Table 3. Plasma and whole-blood APTT ratios are plotted in Figure 2. These ratios were linearly related (estimates slope = 0.56; \( P < 0.001 \)). ACT increased rapidly after RB006 or UFH administration (Figure 3). During PCI, REG1 and UFH achieved similar values, above the desired value of ≥225 seconds, and remained stable in RB006-treated patients but trended upward with UFH.

To evaluate the effectiveness of RB007 in partially or fully reversing RB006 after PCI, plasma APTT, whole-blood APTT, and ACT values were assessed in the partial or total reversal REG1 groups. After PCI, the administration of 0.2:1 drug:control agent dose decreased the plasma APTT ratio from 2.4 to 1.6, the whole-blood APTT value from 145 to 108 seconds, and the ACT value from 237 to 181 seconds in the partial reversal group (Figure 4). As targeted, the median percent reversal of RB006 after the first partial RB007 dose was 48% (25th and 75th percentiles, 38% and 58%), 52% (25th and 75th percentiles, 50% and 69%), and 73% (25th and 75th percentiles, 54% and 84%) for plasma APTT, whole-blood APTT, and ACT. By comparison, a 2:1 active control agent:drug dose administered after the procedure or a second RB007 dose of 1.8:1 administered 4 hours after PCI returned these values to baseline values within 5 minutes, with percent reversal ranging from 95% (25th and 75th percentiles, 78% and 102%) to 112% (25th and 75th percentiles, 104% and 135%), depending on the assay. At 24 hours, coagulation values in the partial reversal, complete reversal, and UFH arms were comparable. Factor IX activity 24 hours after PCI was similar compared with baseline without substantial differences between the REG1 and UFH groups. Safety laboratory data including hematologic and biochemical measurements remained within normal limits without significant fluctuations.

**Pharmacokinetic Measurements**

RB006 measures during PCI were consistent between the REG1 treatment groups. In the partial reversal REG1 group, the mean RB006 plasma concentration was 23.4±7.8 \( \mu \)g/mL 5 minutes after administration and was unchanged during PCI, with a mean concentration of 22.4±8.4 \( \mu \)g/mL after the procedure before RB007 administration. Likewise, in the total reversal REG1 group, the mean RB006 plasma concentration was 25.7±4.9 \( \mu \)g/mL 5 minutes after administration and was unchanged during PCI, with a mean concentration of 25.9±6.0 \( \mu \)g/mL after the procedure before RB007 administration. The measured RB006 concentrations are consistent with the observed elevation of pharmacodynamic measures, which exhibit essentially the maximum expected response to RB006. Administration of a partial reversal (0.2 mg/kg) RB007 dose reduced the mean RB006 plasma concentration to 8.5±2.4 \( \mu \)g/mL 15 minutes after administration. Administration of the second RB007 dose (1.8 mg/kg) further reduced RB006 concentration to below the lower limit of quantification (20 ng/mL) 15 minutes after administration. In the total reversal group, administration of RB007 reduced RB006 concentration to below the lower limit of quantification 15 minutes after administration.

**Clinical Outcomes**

Ischemic events were infrequent, and there were no deaths. The composite of death, MI, and urgent target vessel revascularization occurred in 2 of the 20 patients treated with REG1 and in 1 of the 4 patients treated with UFH. One patient in the partial reversal arm experienced a periprocedural MI after 2-vessel PCI without angiographic complications, ECG changes, or clinical instability. The patient was discharged the following day without any complications.
subsequent events. A patient in the complete REG1 reversal group was readmitted for chest pain 6 days after the index procedure. Repeat coronary angiography demonstrated no evidence of complications at the stented site. However, intravascular ultrasound demonstrated the presence of atherosclerotic disease in a segment proximal to the initial stent. Therefore, an additional stent was placed.

One patient in the UFH group had an uncomplicated enzymatic MI.

There were no angiographic thrombotic complications such as major dissection, abrupt or threatened closure, deterioration of flow, no-reflow, side-branch closure, or distal embolization. Furthermore, there were no reports of thrombus formation in guiding catheters and/or wires.
During the study. There was no need for UFH bailout in any patient, and no vascular-access complications were recorded.

Major and clinically relevant bleeding events were infrequent. One patient in the UFH arm experienced major bleeding within 48 hours of randomization consisting of a groin hematoma >5 cm at the puncture site. Nonserious bleeding occurred in 3 patients treated with REG1 and 1 treated with UFH, all related to vascular access site. None of these met criteria for TIMI major or minor bleeding.

The 2 patients treated in the roll-in group with REG1 received eptifibatide and did not experience any ischemic or major bleeding adverse events. Both patients experienced minimal vascular-access-site bleeds that did not require specific interventions.

Discussion

Our results suggest that nearly complete factor IXa inhibition, achieved with a single intravenous RB006 bolus, can support elective PCI, a finding that has not been documented previously. RB006 provided a rapid, reproducible, and stable pharmacodynamic response that was measurable with a point-of-care coagulation monitoring device used routinely in the catheterization laboratory. This study was the first to investigate the administration of a highly specific and rapid active control agent to achieve a desired intensity of anticoagulation after PCI. Partial reversal of RB006 allowed a graded or “controlled stepdown” in anticoagulation after PCI with a defined sheath removal time, whereas complete RB006 reversal allowed sheath removal immediately after PCI, both without complications.

Factor IXa is a vitamin K–dependent protein and an appealing anticoagulation target. Factor IX is activated early after vascular injury and assembles with factor VIIIa on the platelet surface to form a highly efficient tenase complex, which ultimately results in a burst of thrombin generation required to produce a stable fibrin clot. Factor IXa is a more potent initiator of coagulation than factor Xa or thrombin and is the key driver of factor Xa and thrombin generation during clot propagation.8,15,16 Experimental evidence highlights the role of factor IXa during the initiation of coagulation by the lack of occlusive clot formation in factor IX knockout mice after vascular injury as a result of insufficient generation of thrombin to prime and subsequently form platelet aggregates.17 In animal models of thrombosis, factor IXa inhibition with monoclonal antibodies or competitive antagonism with an active-site–blocked factor IXa prevents arterial thrombosis more effectively and with less bleeding than UFH.18–22 Consis-
tent with this critical role for factor IXa in thrombus formation, transgenic mice overexpressing factor IXa have a shorter lifespan and develop arterial thrombosis and myocardial fibrosis with vascular distribution patterns similar to those of ischemic cardiomyopathy in humans.\textsuperscript{23} In the general population, increased plasma levels of factor IXa are associated with a higher prevalence of cardiovascular risk factors\textsuperscript{24}; higher levels of factor IXa are present in patients with unstable compared with stable coronary artery disease.\textsuperscript{25} It should be noted that RB006 is a highly specific inhibitor of factor IXa, binding to factor IXa \(5000\) fold more tightly than to the structurally related coagulation factors VIIa, Xa, or XIa or activated protein C.\textsuperscript{8,16}

Modeling of the pharmacodynamic and pharmacokinetic data from the evaluation of RB006 and RB007 in phase 1 studies with healthy volunteers and individuals with stable coronary artery disease was predictive of the effects observed in this study. Administration of the \(1\)-mg/kg dose of RB006 achieved the expected \(25\) -\(\mu\)g/mL. RB006 plasma concentrations, resulting in maximal inhibition of factor IX activity as intended and as reflected in the plasma and whole-blood APTT and ACT measures.\textsuperscript{10–12} Administration of the partial reversal dose of RB007 reduced the RB006 plasma concentration to \(\approx 8\) to \(9\) \(\mu\)g/mL, resulting in the intended reversal of \(50\)% of the RB006 anticoagulant effect as measured in the plasma APTT.\textsuperscript{13} Complete reversal doses of RB007 reduced the plasma RB006 concentration to below the limit of quantification and restored coagulation measures to baseline levels.

We demonstrated that the anticoagulant effect of RB006 and reversal activity of RB007 can be measured with APTT and ACT obtained at the bedside with a point-of-care device, thus allowing real-time monitoring of anticoagulation during PCI. The implication of this finding is significant for the potential adoption of the REG1 system in clinical practice. ACT monitoring during PCI has been used for decades and provides the needed reassurance to interventional cardiologists before instrumenting a coronary artery. The inability to easily monitor the pharmacodynamic response of low-molecular-weight heparin has hampered its adoption in clinical practice.

The only active anticoagulation reversal agent currently available is protamine, a highly cationic polypeptide that binds to UFH and neutralizes its activity. Protamine is not titratable and can induce direct mast cell degranulation, complement activation, and antibody formation, leading to potentially catastrophic adverse reactions such as myocardial depression, cardiac arrest, bronchospasm, pulmonary hypertension, pulmonary edema, and vasodilatory shock.\textsuperscript{26} Systematic reversal with protamine after PCI has not been widely adopted because of its toxicity profile, and its use is reserved for severe life-threatening vascular perforations.\textsuperscript{27} Phase 1 studies have demonstrated that RB007 is well tolerated and have not suggested an association between RB006 reversal and “rebound” thrombin generation. Through highly selective binding of RB006, RB007 restores factor IX activity to preexisting levels and is not anticipated to increase thrombosis risk. We observed that factor IX levels were similar and within normal limits before and 24 hours after PCI despite a cycle of drug–reversal agent administration.

In principle, the properties of REG1 elucidated in the 3 phase 1 studies and present phase 2a study underscore the inherent shortcomings of both heparins and bivalirudin in PCI. The rapid onset and low variability of anticoagulant response to RB006 permit precise dosing. The long half-life of RB006 allows single intravenous bolus dosing before PCI with consistent anticoagulation throughout the procedure, potentially reducing monitoring needs. RB007 provides a readily available means for controlled post-PCI reversal of RB006, facilitating scheduled, and potentially early, removal of the femoral arterial sheath.
Conclusions
The conduct of elective PCI is feasible and well tolerated with REG1. An anticoagulation strategy through factor IXa inhibition with RB006, followed by an active reversal strategy with RB007, may favorably shift the balance of safety and efficacy during PCI, wherein a period of heightened thrombotic potential coexists with a need for effective hemostasis. An ongoing randomized phase 2b study, partially-blinded, multicenter, active-controlled, dose-ranging study assessing the safety, efficacy, and pharmacodynamics of REG1 compared with heparin, will provide valuable experience in patients with non–ST-elevation acute coronary syndromes undergoing PCI. (RADAR; NCT00932100)

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References
CLINICAL PERSPECTIVE

Anticoagulants for percutaneous coronary intervention (PCI) are limited by unpredictable pharmacodynamics and/or lack of active reversibility. The REG1 system is an oligonucleotide RNA aptamer pair comprising the direct rapid-onset factor IXa inhibitor RB006 and its active dose-dependent control agent RB007. REG1 offers effective, predictable, and reversible anticoagulation. We assessed whether anticoagulation through factor IXa inhibition with RB006 could support low- to moderate-risk PCI. This phase IIa study enrolled 26 patients undergoing elective PCI. In a roll-in group, 2 patients received REG1 and glycoprotein IIb/IIIa inhibitors. Then, 24 patients were randomized 5:1 to REG1 (n=20) or unfractionated heparin (n=4). REG1 patients received RB006 (1 mg/kg) after arterial access. In the first 10 REG1 patients, RB007 was dosed to partially reverse RB006 by 50% after PCI and to completely reverse RB006 at 4 hours. In the subsequent 10 REG1 patients, RB007 was dosed once to completely reverse RB006 immediately after PCI. All PCI procedures were successful without angiographic procedural thrombotic events or catheter thrombus, and bleeding was infrequent. Baseline plasma and whole-blood activated partial thromboplastin time increased by 2.5- and 1.8-fold 5 minutes after RB006 but trended upward with unfractionated heparin. Partial RB007 reversal reduced RB006 activity by 51±14% to 68±15%. Complete reversal reduced RB006 activity by 93±11% to 103±13%, depending on the assay. Anticoagulation through factor IXa inhibition with RB006, followed by active reversal with RB007, was feasible and may favorably shift the balance of safety and efficacy during PCI.
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